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Regulation of T_H17 cell differentiation by innate immune signals

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Abstract

Upon antigen stimulation, naïve T helper cells differentiate into distinct lineages to attain specialized properties and effector functions. T_H17 cells, a recently identified lineage of $CD4^+$ effector T cells, play a key role in the immune defense against fungi and extracellular bacteria but also contribute to the pathogenesis of many autoimmune conditions. The differentiation of T_H17 cells is orchestrated by an intricate network of signaling pathways and transcriptional regulators in T cells. While the involvement of T cell-intrinsic pathways has been described extensively, we are just beginning to appreciate how T_H17 cell development is shaped by extrinsic pathways especially the innate immune signals. Dendritic cells (DCs), the most important cell type to bridge innate and adaptive immunity, drive T_H17 cell differentiation by providing antigenic, costimulatory and cytokine signals. This is mediated by the recognition of innate and inflammatory signals by DCs *via* pattern recognition receptors, cytokine receptors and other immunomodulatory receptors that in turn activate the intracellular signaling network. In particular, p38α MAP kinase has emerged as a critical pathway to program DC-dependent T_H17 cell differentiation by integrating multiple instructive signals in DCs. Here we summarize the current knowledge on the mechanisms by which DC-derived innate immune signals drive T_H17 cell differentiation.

Keywords

dendritic cells; innate immunity; MAPK; T cell differentiation; T_H17 cells

INTRODUCTION

For more than twenty years, it has been appreciated that naïve $CD4^+$ T cells can differentiate into distinct lineages to attain specialized properties and effector functions. For the initially identified T cell subsets, T_H1 cells are characterized by high production of IFN-γ and are necessary to clear intracellular pathogens. T_H2 cells produce the signature cytokine interleukin-4 (IL-4) and are effective at controlling helminthes[1]. A new subset of IL-17-producing T (T_H17) cells has recently been described to mediate immune defense against fungi and extracellular bacteria and tissue inflammation in autoimmune diseases. T_H17 cell differentiation can be initiated by transforming growth factor-beta (TGF-β) in the presence of inflammatory cytokines IL-6 or IL-21, and is further reinforced by IL-23. T_H17 cells produce several signature cytokines including IL-17, IL-17F and IL-22, which provoke inflammatory responses including neutrophilia, tissue remodeling, and production of antimicrobial proteins[2-5]. In the absence of the proinflammatory inputs, TGF-β drives naïve

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$CD4^+$ T cells to develop into induced $Foxp3^+$ regulatory T (iT_{reg}) cells, which act in synergy with natural T_{reg} (nT_{reg}) cells to promote immune tolerance and inhibit autoimmunity[5]. Although the presence of additional T cell subsets and the plasticity of T cell lineage choices have been appreciated, these four T cell populations represent the widely accepted major T cell lineages (Figure 1). The specification of T cell lineages is orchestrated by an intricate network of signaling pathways and transcriptional master regulators in T cells. While the involvement of T cell-intrinsic pathways has been described extensively, how T cell differentiation is triggered by extrinsic pathways and physiological stimuli is relatively less understood.

Antigen-presenting cells (APCs) drive T cell differentiation by providing the antigenic, costimulatory and cytokine signals. DCs are the most important APCs to bridge the crosstalk between innate and adaptive immunity[6, 7]. DCs express a repertoire of pattern recognition receptors (PRRs) that sense microbial pathogen products and endogenous ligands to initiate a signaling cascade culminating in the activation of DCs and induction of adaptive immunity. Activated DCs present high levels of major histocompatibility complex (MHC) molecules bearing pathogen-derived peptides, which engage T cell receptors (TCRs) on naïve antigen-specific T cells. This delivers the first activating signal to the T cell and is therefore referred to as ‘signal 1’. DCs activated by pathogen encounter also upregulate costimulatory molecules to bind counter-receptors on T cells and transmit signals that are important for T cell proliferation and survival (signal 2). Finally, activated DCs also produce cytokine and non-cytokine mediators that act on the T cell to promote its differentiation into an effector cell (signal 3). The integration of these three classes of signals by the responding T cells, to a large extent, determines their subsequent fate.

In this review, we summarize the recent findings on the mechanisms by which DC-mediated innate immune signals drive T_H17 cell differentiation and inflammation. We first provide a brief overview of intrinsic pathways, especially transcriptional mechanisms, that specify the T_H17 lineage choice. We then discuss how DC-derived immune signals, especially the polarizing cytokines, mediate T_H17 cell differentiation by shaping the interface between DCs and T cells. We next describe how receptor-specific signals instruct DCs to drive T_H17 cell differentiation, by focusing on the roles of PRRs and other immunomodulatory receptors expressed by DCs. Finally, we highlight the emerging data that the stress-activated p38 MAP kinase (MAPK) pathway integrates diverse instructive signals in DCs for T_H17 cell differentiation.

INTRINSIC CONTROL OF T_H17 CELL DIFFERENTIATION: AN OVERVIEW

Since the seminal discovery of T_H17 cells as a separate lineage[8, 9], multiple transcription factors have been identified as critical regulators of T_H17 cell differentiation[10]. Among the lineage-restricted transcription factors essential for T_H17 cell differentiation are two retinoic acid-related organ receptors, RORγt and RORα[11, 12]. Similar to T-bet in T_H1 cells and GATA3 in T_H2 cells, RORγt and RORα are highly induced in TH17 cells and play central roles in specifying the lineage differentiation. Overexpression of either transcription factor promotes T_H17 cell differentiation when T_H1 and T_H2 differentiation is blocked. Deficiency of RORγt, and to a considerably lesser extent, of RORα, impairs T_H17 cell differentiation, whereas loss of both factors completely inhibits T_H17 cell differentiation and suppresses the development of experimental autoimmune encephalitis (EAE), a T_H17-mediated autoimmune disease[11, 12]. Thus, RORγt and RORα have redundant functions, with RORγt playing a more dominant role in specifying the T_H17 cell fate.

Induction of RORγt and RORα under T_H17-polarizing conditions is dependent upon STAT3, which perceives and transduces signals from IL-6, IL-23 and other cytokines.

Deficiency of STAT3 decreases the expression of lineage-specific transcription factors and the T_H17 family cytokines, whereas enhancing STAT3 activity *via* deletion of the negative regulator SOCS3 increases IL-17 expression[13-15]. Aside from RORγt, RORα and STAT3, additional transcriptional factors contribute to T_H17 cell differentiation and/or cytokine expression. These include IRF4[16], BATF[17], RUNX1[18], and c-Maf[19], most of which have additional roles in other aspects of T cell lineage choices in the periphery or thymus. Finally, T_H17 cell differentiation is further shaped by transcription factors with prominent roles in environmental sensing. Two of the most notable examples are AHR and HIF1α, which sense environmental toxins and hypoxic conditions, respectively[20–23]. Therefore, differentiation of T_H17 cells requires coordinated actions of multiple transcription factors. These transcriptional mechanisms act in synergy with the signaling networks, metabolic pathways and epigenetic regulators to perceive and transduce diverse lineage specification signals derived from DCs.

IMMUNE SIGNALS AT THE DC–T CELL INTERFACE FOR T_H17 POLARIZATION

DCs are the most potent cell type to deliver antigens, costimulation and cytokines to T cells for their proper activation and differentiation. As compared with the development of other T cell lineages, differentiation of T_H17 cells has selective requirements for DC-derived signals. The integration of these external signals by T cells ultimately dictates the quality and quantity of T_H17-mediated immune responses (Figure 2).

Antigenic signals

It has been known for some time that fate determination of T cells is shaped by the strength of TCR signals. Specifically, high antigen doses promote the generation of T_H1 cells, whereas low doses of the same antigen favor T_H2 cell polarization[24, 25]. The effects of antigen doses were later found to correlate with the extent of CD40L upregulation on T cells[26]. Iezzi *et al.* recently reported that the strength of antigenic stimulation also critically influences T_H17 cell differentiation, because high, but not low or intermediate, antigen concentrations favor IL-17 production[27]. Strong antigenic stimulation of T cells upregulates CD40L expression, which acts in concert with certain microbial stimuli to enhance IL-6 production from DCs to drive T_H17 polarization. Compared with T_H1 cells, T_H17 cells appear to require even stronger antigen stimulation for their development, and this is associated with profound upregulation of CD40L expression on T cells that in turn delivers CD40L–CD40-mediated costimulation to DCs[27]. Indeed, CD40 deficiency diminishes IL-6 production from DCs and markedly reduces T_H17 responses in models of EAE and stimulation with the Gram-positive bacterium *Propionibacterium acnes*[27, 28]. We also observed defective T_H17 cell differentiation mediated by CD40-deficient DCs *in vitro*, suggesting the involvement of direct DC and T cell interaction[29]. Therefore, high antigen concentrations favor T_H17 cell differentiation by fostering the CD40L–CD40 cross-talk at the DC–T cell interface.

Costimulatory molecules

DCs express a number of costimulatory molecules including CD80 (B7-1) and CD86 (B7-2) on their cell surface to engage the corresponding receptors, such as CD28, on T cells. This interaction transmits signals to promote T cell proliferation and survival. Park *et al.* reported that APCs deficient in both B7 molecules failed to instruct T cell differentiation into T_H17 cells[8]. Odobasic *et al.* later demonstrated that inhibition of CD86, but not CD80, suppressed IL-17 production from splenocytes and decreased T cell accumulation in the joints in the model of antigen-induced arthritis[30]. Consistent with this, our recent study indicated that blocking CD86 function downregulated DC-dependent T_H17 cell differentiation *in vitro*[29].

Conversely, CTLA4, a negative factor for T cell activation that also interacts with B7 molecules on DCs, inhibits T_H17 cell differentiation *in vitro* and *in vivo* and suppresses T_H17-mediated autoimmunity[31]. The inducible costimulatory ICOS is another member of the CD28 superfamily that also regulates naïve T cell activation. ICOS signaling in T cells is required for efficient T_H17 development and expansion in both murine and human systems[8, 32], indicating the therapeutic potentials of ICOS modulation for the treatments of T_H17-dependent disorders. ICOS functions by inducing c-Maf and transactivating IL-21, an important T cell autocrine factor for T_H17 cell differentiation[19]. These findings collectively indicate that T_H17 cell differentiation requires selective costimulatory signals from DCs.

Polarizing cytokines

Among the most potent factors to polarize T_H17 cell differentiation are STAT3-activating cytokines IL-6, IL-21 and IL-23, along with TGF-β and IL-1. IL-6, IL-23 and IL-1 are mainly produced by the innate immune system especially DCs, whereas IL-21 and TGF-β can be produced by T cells in an autocrine/paracrine manner to further shape T_H17 cell development. Earlier studies showed that IL-17-producing cells could be efficiently generated *in vitro* from naïve $CD4^+$ T cells activated with TCR and costimulation in the presence of IL-6 and TGF-β[33–35]. Although less effective than IL-6 in initiating T_H17 cell differentiation, IL-21 produced by developing T_H17 cells has an important role to propagate the differentiation process[15, 36, 37]. In contrast to IL-6, IL-23 does not act on naïve T cells, because the receptor for IL-23 is induced only in T cells after stimulation in the presence of IL-6 or IL-21. Therefore, IL-23 is more important in the later phase of T_H17 cell differentiation and in the maintenance of the T_H17 phenotype[38]. However, this function of IL-23 is indispensable for the pathogenicity of T_H17 cells, as mice lacking IL-23 are completely resistant to EAE[39]. The roles of IL-23 signaling in the development of human T_H17-related autoimmune diseases were further highlighted by recent findings showing the association of IL-23R polymorphisms and the prevalence of several autoimmune diseases[40]. Therefore, the three STAT3-activating cytokines IL-6, IL-21 and IL-23 are critically involved in the initiation, amplification and stabilization stages of T_H17 cell differentiation, respectively. Another proinflammatory cytokine, IL-1, also pays a crucial role in early T_H17 cell differentiation by signaling through IL-1R1 and the downstream Myd88–TRAF6 pathway to promote IRF4 and RORγt expression in T cells[41, 42].

Compared with the well described roles of these proinflammatory cytokines in T_H17 responses, whether and how the immunosuppressive cytokine TGF-β regulates T_H17 cell differentiation remain incompletely understood. Addition of TGF-β to IL-6 or IL-21 enhances the development of T_H17 cells *in vitro*[15, 36, 37], and deletion of TGF-β1 specifically from T cells lowers T_H17 cell generation and EAE[43]. Moreover, phagocytosis of infected apoptotic cells by DCs triggers the release of both IL-6 and TGF-β to instruct T_H17 cell differentiation during infection[44]. However, high doses of TGF-β downregulate the expression of IL-23R, the key pathogenic molecule associated with T_H17 cells, and instead provoke Foxp3 expression and iT_{reg} induction[45]. Further, Ghoreschi *et al.* described the generation of T_H17 cells that are mediated by IL-6, IL-23 and IL-1β in the complete absence of TGF-β signaling. Compared with T_H17 cells derived from IL-6 and TGF-β, the TGF-β-independent T_H17 cells exhibit distinct expression profiles and more importantly, stronger pathogenicity in the EAE model[46]. These results highlight the heterogeneity of T_H17 responses and context-dependent effects of TGF-β on T cell fate decision. Equally complex is the source(s) of TGF-β to drive T_H17 responses. Although TGF-β derived from T_{reg} cells was initially thought to promote T_H17 cell differentiation[33], recent genetic studies highlighted an important role of TGF-β1 produced by activated T cells, but not T_{reg} cells, to promote T_H17 responses[47]. Moreover, DCs were also shown to be an important source of TGF-β for T_H17 cell differentiation[48]. Consistently with this notion, expression of the

integrin αvβ8, which is required to activate TGF-β, plays a critical role in the differentiation of T_H17 cells[49, 50]. Additional studies are required to ascertain the precise function and regulation of TGF-β in T_H17 cell differentiation.

T_H17 cell differentiation is shaped by both positive and negative polarizing cytokines. IL-27 is arguably the most potent cytokine produced by DCs to limit T_H17 cell differentiation and autoimmune inflammation. Mice deficient in IL-27R are hyper-susceptible to EAE and other inflammatory disorders and generate more T_H17 cells[51–53]. Multiple mechanisms mediate the effects of IL-27 for the inhibition of T_H17 cell development[54]. A particularly important mechanism is IL-27-dependent induction of IL-10-expressing Tr1 cells that play a central role in downregulating the proinflammatory T_H17 cell responses[55–57]. Furthermore, IL-27 inhibits T_H17 cell differentiation *via* directly inhibiting RORγt and RORα expression and promoting T-bet expression and T_H1 generation[54]. In addition to IL-27, production of IL-10 by DCs has also been shown to inhibit T_H17 cell differentiation *via* constraint of IL-1 production by DCs[58]. Several T cell-derived cytokines, such as IFN-γ, IL-4 and IL-2, have also been shown to inhibit T_H17 cell development[8, 9, 59, 60]. Since DCs are not the major producer of these cytokines, such regulation is not further discussed here. The readers are encouraged to read excellent reviews on this topic[2–5].

In summary, differentiation of T_H17 cells is largely determined by the innate immune signals transduced from DCs and the integration of these signals by responding T cells. In particular, DC-derived cytokines deliver a critical 'signal 3' to T cells, to mediate both positive and negative regulation of T_H17 cell differentiation. Aside from antigens, costimulation and cytokines, recent work has identified that differentiation of T_H17 cells is influenced by additional immune modulators produced by DCs. For example, retinoic acid, a vitamin A metabolite produced by $CD103^+$ DCs in the gut-associated lymphoid tissues (GALTs), inhibits T_H17 cell differentiation while promoting iT_{reg} generation by activating the retinoic acid receptor[61–63]. Moreover, while the crosstalk between DC and T cells plays a central role in programming T_H17 cell differentiation, additional cell types modulate functions of DCs and T cells and/or the immune microenvironment to impinge upon T_H17 cell differentiation. In this context, mice deficient for γδ T cells have markedly attenuated T_H17-mediated autoimmune disease[64]. Mechanistically, IL-17 expressed by this lymphocyte subset activates IL-17R on epithelial and stromal cells, resulting in the production of IL-6, IL-1 and other inflammatory cytokines that act in a positive feedback loop on the γδ T cells and differentiating T_H17 cells to amplify inflammation[5, 64].

SENSING T_H17-INSTRUCTIVE STIMULI BY DC RECEPTORS

In agreement with a potent proinflammatory function of T_H17 cells, T_H17-mediated responses are strongly induced in models of autoimmune and infectious diseases. van de Veerdonk *et al.* directly compared the effects of different pathogens to elicit T_H17 responses, and found that the fungus *Candida albicans* was much more potent than various bacteria tested to induce IL-17 production from human PBMC[65]. We also found that heat-killed fungi had much greater adjuvant activity than bacteria to stimulate antigen-specific T cells to differentiate into T_H17 effector cells *in vivo*[29]. Further, under steady-state conditions, a sizable population of $IL\text{-}17^+$ $CD4^+$ T cells is detectable in GALTs such as lamina propia from small intestine in response to commensal microbiota[66]. How do the diverse innate stimuli and microbial agents instruct T_H17 responses? PRRs expressed by DCs, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and NOD-like receptors (NLRs), are essential to sense these T_H17-instructive stimuli. Cytokine receptors and other immunomodulatory receptors also contribute to DC-mediated T_H17 cell differentiation (Figure 2). Here we summarize the functions of these receptors, including

mechanisms by which these receptors transduce signals *via* receptor-proximal downstream signaling.

TLRs

TLRs, the first group of PRRs identified, are classically considered to polarize toward T_H1 responses[67]. Recent studies indicate that ligation of certain TLRs on DCs potentiates T_H17 cell differentiation by affecting production of T_H17-polarizing cytokines[27, 68, 69]. TLR-mediated effects on T_H17 responses are generally much weaker than those induced by CLRs (see below for details)[70, 71]. Further, several TLRs, including TLR2, TLR6 and TLR7, have been implicated in negatively regulating T_H17 responses in inflammatory and infectious models[72–75]. This is associated with the abilities of these receptors to downregulate IL-23 production from DCs. Therefore, TLR signaling in DCs can either positively or negatively regulate T_H17 cell differentiation, in a receptor and stimulation-specific manner. It should also be noted that T cells themselves express TLRs and respond to TLR stimulation. T cells stimulated with TLR2 agonists exhibit enhanced T_H17 cell differentiation, and loss of TLR2 in $CD4^+$ T cells ameliorates EAE[76]. The cell type-specific roles of TLRs in T_H17 cell differentiation require additional studies, which can be assisted with the generation and analysis of conditional alleles of these receptors.

CLRs

CLRs are a large family of proteins characterized by the presence of one or more C-type lectin-like domains (CTLDs). Several CLRs recognize carbohydrates in the cell wall of fungi and other pathogens (such as β-glucans) and signal through the intracellular kinase Syk to initiate inflammatory responses in both innate and adaptive immunity[77]. Ligation of these CLRs on DCs is an important mechanism by which fungal infection induces strong T_H17 cell responses. LeibundGut-Landmann *et al.* reported that the prototypical CLR, Dectin-1 (also known as CLEC7a), activates Syk and the adaptor CARD9 to promote DC maturation and production of T_H17-polarizing cytokines, thereby instructing T cell differentiation into the T_H17 lineage. Infection with *C. albicans* induces CARD9-dependent T_H17 responses and protective immunity[70]. Further studies showed that Dectin-2 (CleC6A), which also signals through Syk and CARD9, is even more potent than Dectin-1 to mediate T_H17 cell responses and protection from *C. albicans* infection[78, 79]. Moreover, mannose receptor, another member of the CLR family, is also important to induce IL-17 production in response to *C. albicans*[65]. These results collectively highlight potent effects of CLRs in driving T_H17 responses. Moreover, synergic interactions between CLRs and TLRs further modulate T cell fate[79, 80].

NLRs

NLRs are a family of innate immune receptors for intracellular microbial sensing characterized by the presence of a conserved NOD domain[81]. NLRs are implicated in a multitude of innate immune signaling pathways ranging from the regulation of MAPK and NF-κB signaling pathways by NOD1 and NOD2, to the assembly of caspase-1-activating protein complexes named ‘inflammasomes’ by the NLR protein NLRP3[81]. Recent studies have identified important roles for NLRs to bridge innate and adaptive immunity by promoting T_H17 cell differentiation. NOD1 and NOD2, members of the NLR family, detect muramyldipeptide (MDP), a derivative of bacterial peptidoglycan and signal through downstream kinase RIP2. Activation of NOD2 synergizes with TLR ligation to induce DC production of IL-23 and IL-1 that drive T_H17 cell responses in human memory T cells. NOD2-deficient DCs, such as those from Crohn's disease patients, are defective to engage the IL-23–IL-1–IL-17 axis[82]. Moreover, mice deficient in NOD1, NOD2 or RIP2 are resistant to EAE, associated with diminished activation of CNS-infiltrating DCs and IL-17 expression from CNS T cells[83]. Aside from the NOD proteins, NLRP3-mediated

inflammasome complex, which activates caspase-1 to process pro-IL-1β and pro-IL-18, has been shown to regulate T_H17 cell generation. Deficiency of NLRP3, the downstream adaptor ASC, or caspase-1 ameliorates EAE pathogenesis. Mechanistically, this is linked to the requirement of NLRP3 to promote IL-1 and IL-18 production from DCs for the potentiation of T_H17 responses[84–86]. The role of NLRP3 to mediate DC-dependent T_H17 cell responses has also been observed in infection models of *Bordetella pertussis* and *C. albicans*[87,88]. Conversely, hyperactivation of NLRP3 causes excessive IL-1β production from APCs, leading to augmented T_H17 cell differentiation and T_H17 cell-dominant immunopathology[89]. Therefore, activation of NLPR3-mediated inflammasome by DCs promotes T_H17 cell differentiation *via* IL-1β and/or IL-18 in autoimmune, infectious and inflammatory models.

Cytokine receptors

In addition to recognizing microbial products through PRRs, DCs sense signals transduced from cytokines. The proinflammatory cytokine TNF-α promotes DC production of IL-23, whereas blocking TNF-α activity suppresses T_H17 responses and inflammation in psoriasis patients[90]. The receptor for stem cell factor (SCF), c-Kit (a receptor tyrosine kinase), is upregulated on DCs by T_H17 and T_H2-skewing stimuli such as allergens and allergy-inducing adjuvants, but not by T_H1-inducing adjuvants[91]. Upregulation of c-Kit on DCs results in PI3K activation and elevated IL-6 secretion that in turn promotes T_H17 and T_H2 cell differentiation. DCs expressing nonfunctional c-Kit are unable to induce robust T_H17 and T_H2 responses and airway inflammation, highlighting the importance of the c-Kit–PI3K–IL-6 signaling axis in DCs in instructing T_H17 responses[91].

Conversely, IFN-β, an effective therapy against relapsing-remitting multiple sclerosis, has recently been shown to suppress T_H17 cell differentiation by altering the production of T_H17-polarizing cytokines from DCs[92–94]. Engagement of type I IFN receptor (IFNAR) by IFN-β on DCs prevents the expression of an intracellular isoform of osteopontin, termed iOpn, an inhibitor of IL-27. Mice containing DC deficient in iOpn produce excessive amounts of IL-27 and develop a delayed EAE disease associated with diminished IL-17 responses. These studies identify an IFNAR-iOpn axis that restrains T_H17 cell development[93]. However, it should be noted that IFN-β is ineffective and might worsen clinical status in multiple sclerosis and other diseases when a T_H17 immune response is prominent[95, 96]. This probably reflects the effects of IFN-β on cells other than DCs, and highlights the complex roles of IFNAR in the pathogenesis and treatment of autoimmune diseases. Interestingly, ligation of IFN-γ receptor (IFNGR) expressed by DCs leads to suppression of IL-17 production while inducing IL-10 from T cells, and this is mediated by the ability of IFN-γ to induce the expression of IL-27 but inhibit that of the secreted form of osteopontin[97, 98]. Cytokine receptor signaling in DCs therefore shapes differentiation of T_H17 cells.

Receptors for additional immune modulators

DCs employ additional receptors to link inflammatory and environmental cues to proper T cell lineage decision. Ligation of CD40 on DCs by T cell-expressed CD40L endows DCs with the ability to promote T_H17 cell differentiation *via* IL-6[27, 28]. Stimulation of the chemokine receptor CCR7 by its ligands promotes the expression of IL-23 from DCs and IL-23-dependent generation of pathogenic T_H17 cells in EAE[99]. Adenosine is an endogenous metabolite produced during hypoxia or inflammation. Recent studies indicate that adenosine acts *via* A_{2B} adenosine receptor on DCs to promote IL-6 expression and development of T_H17 cells[100]. PGE_2, a major lipid mediator released in inflammatory conditions, induces IL-17 production in activated T cells in the model of inflammatory bowel disease (IBD). PGE_2 signals through the EP2/EP4 receptors on DCs to shift the

IL-12/IL-23 balance in DCs in favor of IL-23[101]. Analysis of mice deficient in EP2 or EP4 reveals that PGE_2 facilitates T_H17 cell generation in EAE redundantly through these two receptors[102].

As described above, AHR acts in a T cell-intrinsic manner to modulate T_H17 cell differentiation[20, 21]. Interestingly, AHR was recently shown to negatively regulate DC immunogenicity by inducing expression of IL-10 and indoleamine 2,3-dioxygenase (IDO), an immunosuppressive enzyme[103]. Absence of AHR in DCs inhibits iT_{reg} development and facilitates T_H17 cell generation from naïve T cells[103], whereas DCs activated with AHR suppresses EAE upon transfer[104]. Another DC pathway negatively regulating T_H17 cell responses is mediated by the Wnt-Frizzled (fzd) receptor and the downstream β-catenin signaling. Manicassamy *et al.* reported that DC-specific deletion of β-catenin disrupts intestinal homeostasis and results in lower frequency of T_{reg} cells but increased percentages of effector T_H17 and T_H1 cells[105]. Deficiency of β-catenin in DCs alters the balance of proinflammatory and anti-inflammatory cytokines and exacerbates the inflammatory response in an IBD model, highlighting that β-catenin signaling in DCs promotes intestinal homeostasis and tolerance[105]. Therefore, diverse receptors in DCs translate inflammatory mediators and environmental cues into proper T_H17 cell generation.

In summary, DCs sense pathogenic agents, immune stimuli and environmental cues through a plethora of receptors. In each case, the ligand and receptor interaction initiates a specific signaling cascade in DCs culminating in the expression of T_H17- polarizing cytokines and other factors, which then positively or negatively modulate T_H17 cell differentiation. In general, activation of DC receptors induces simultaneous development of multiple T cell subsets, not just T_H17 cells alone. Given the well described cross regulation between T cell subsets[3–5], whether T_H17 cell differentiation is directly or specifically shaped by the signals transduced from DC receptors requires additional studies in many contexts. Moreover, it remains poorly understood how the kaleidoscopes of innate signals are integrated to shape T cell fate decision. Although different mechanisms are likely to exist, we have recently identified that p38α MAPK signaling serves as an important converging point in DCs to integrate these diverse signals to mediate T_H17 responses, which is further discussed below.

BRIDGING INNATE AND T_H17 IMMUNITY BY p38/MKP-1 SIGNALING IN DCs

Among the central pathways activated by innate and inflammatory stimuli in DCs is MAPK signaling. MAPKs, comprised of ERK, JNK and p38, represent a fundamental and evolutionarily conserved mechanism for cellular responses to a wide range of extracellular signals[106]. Excessive activation of MAPKs is associated with many autoimmune and inflammatory diseases, and inhibitors of these pathways have been evaluated as new therapeutics for these disorders[107]. As a matter of fact, among all of the protein kinase targets for the development of anti-inflammatory drugs in the pharmaceutical industry, p38α MAPK is by far the most extensively investigated protein, but severe side effects have prevented clinical advancement of many p38α inhibitors[107]. In DCs, p38α is expressed at much higher levels than the other three p38 isoforms (p38β, γ and δ). Importantly, p38 activation is greatly elevated in DCs treated with various types of T_H17-instructive signals (including engagements of Dectin-1 and CD40 receptors and stimulation with heat-killed *C. albicans*), relative to T_H1-polarizing stimuli. These findings suggest a potential role for p38α to mediate DC-dependent T_H17 cell differentiation by integrating T_H17-instructive signals (Figure 3)[29].

To dissect the selective role of p38α in DCs, we generated mice with DC-specific deletion of p38α and established a central role for p38α to program DC-dependent T_H17 cell differentiation and autoimmune CNS inflammation[29]. p38α in DCs mediates reciprocal

regulation of IL-6 and IL-27, arguably the most potent positive and negative regulators of T_H17 polarization, respectively, and further imprints STAT3 signaling and IL-23R expression in responding T cells. Additionally, p38α is important for optimal CD86 expression on DCs and shapes strength of the costimulatory signals, thereby orchestrating a program for DC-dependent T_H17 cell differentiation. Moreover, p38α is required for tissue-infiltrating DCs to sustain T_H17-dependent neuroinflammation, and also contributes to T_H17 cell generation in response to commensal microbiota and fungal infection. Mechanistically, p38α integrates diverse T_H17-instructive signals (TLRs, CLRs and CD40) in DCs and further links them to a core set of downstream signaling and transcriptional regulators for the expression of DC-derived 'signals 2 and 3'. These findings identify p38α signaling as a central pathway for the integration of instructive signals in DCs for T_H17 cell differentiation and inflammation[29].

Negative regulation of MAPK activity is effected primarily by MAPK phosphatases (MKPs), a group of over 10 dual-specificity phosphatases that dephosphorylate the MAPK on their regulatory threonine and tyrosine residues. MKP-1 (DUSP1), the protypical member of this family, is a key negative regulator of innate immune responses by limiting the activation of MAPKs[108]. DCs lacking MKP-1 exhibit higher activity of p38, and to a lesser extent, JNK[71]. These mutant DCs show increased ability to drive T_H17 cell differentiation but are defective to mediate T_H1 cell differentiation, suggesting that MKP-1 signaling in DCs programs reciprocal T_H1 and T_H17 cell differentiation. This is mediated by the effects of MKP-1 to modulate the IL-12/STAT4 and IL-6/STAT3 axes at the DC–T cell interface, and T cell expression of IL-12Rβ2 and IL-23R (which pair with IL-12Rβ1 to constitute functional IL-12 and IL-23 receptors, respectively). Deficiency of MKP-1 in innate immune cells disrupts *in vivo* immune responses against infections and immunization and promotes T cell-mediated inflammation. Moreover, MKP-1 inhibits induction of iT_{reg} cells by downregulating TGF-β2 production from DCs. Our findings identify a regulatory circuit linking MKP-1 signaling in DCs, production of immunomodulatory cytokines, and integration of DC-derived signals *via* STAT activation and cytokine receptor expression in T cells, that bridges innate and adaptive immunity and coordinates protective immunity and immunopathology[71].

Notably, whereas MKP-1 and p38α in DCs have reciprocal effects on T_H17 cell differentiation, deficiency of MKP-1 also impairs T_H1 cell generation but p38α does not play a crucial role in this process[29, 71]. These results highlight the complex interactions between MKP-1 and p38α. For example, MKP-1 inhibits JNK as well as p38, but also depends upon p38 for its transcriptional induction[109, 110]. Altogether, our studies identify the MKP-1/p38α axis as a key mechanism of DC-mediated programming of T_H17 cell differentiation (Figure 3), and lend strong rationale for therapeutic modulation of this pathway in DCs as a potential treatment for autoimmune conditions mediated by T_H17 cells[29, 71].

CONCLUDING REMARKS

Dependence of T cell-mediated adaptive immunity on innate immune signals and DCs has been known for a long time[111], and the identification of TLRs and other PRRs has revolutionized our understanding of immune responses[6]. More recent studies have demonstrated that engagements of PRRs and other receptors endow DCs with the ability to shape the differentiation of T_H17 cells, one of the most proinflammatory cell types. While recognition of innate and inflammatory stimuli begins at the receptor level, it is the signaling components downstream of each receptor and the way they interact with each other that ultimately determines the specific immunological outcome. The identification of p38α signaling as a key mechanism to integrate T_H17-instructive signals in DCs has contributed

to our understanding of the crosstalk between innate and adaptive immunity. Many open questions remain in this exciting area. Current studies of T_H17 responses are mainly focused on the induction of these cells during inflammatory responses and autoimmune diseases. How DCs are involved in the generation of T_H17 cells mediated by commensal microbiota under steady state remains poorly understood[66]. Similarly, whether DCs regulate the differentiation of T_H17 cells in the thymus[112], as well as of other IL-17-producing cells such as γδ T cells and innate lymphoid cells[113], has yet to be determined. As for the molecular pathways in DCs, the development of CD11c-Cre mice for DC-specific gene targeting has been instrumental to our understanding of DC-mediated innate and adaptive immunity[114]. We anticipate the extensive use of this approach to address DC pathways for *in vivo* T_H17 responses in the near future. However, given the heterogeneity of DC populations, the CD11c-Cre system does not allow the analysis of all DC subsets *in vivo*. More sophisticated strategies to target DCs are required to fully appreciate how DC-mediated innate signals mediate adaptive immunity and T_H17 cell differentiation. Addressing this issue is not only insightful to understanding fundamental mechanisms of immune regulation, but is also relevant to the investigations of disease mechanisms and therapeutic interventions of a number of autoimmune and inflammatory disorders.

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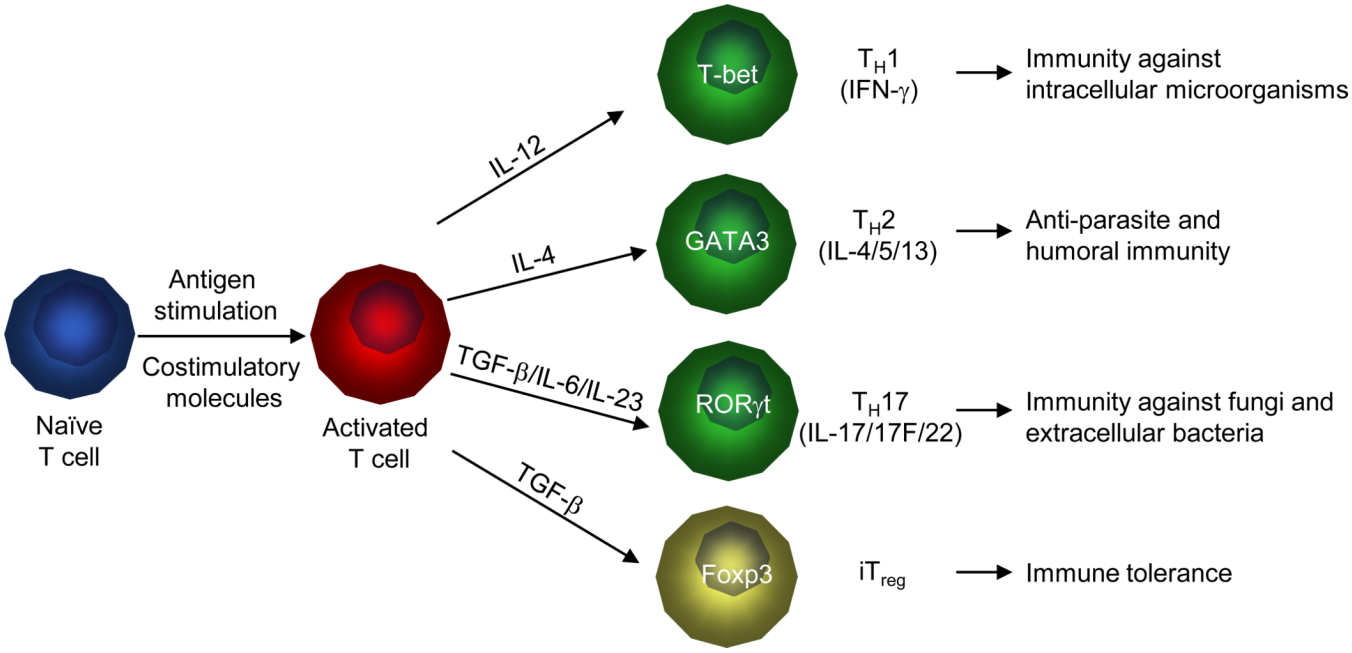

Figure 1. T cell lineage commitment and function

Upon encountering foreign antigens and costimulatory molecules presented by DCs, naïve $CD4^+$ T cells can differentiate into T_H1, T_H2, T_H17 and iT_{reg} cells. These differentiation programs are mainly shaped by cytokines produced by DCs and are characterized by the expression of lineage-specific transcription factors and production of signature cytokines. IL-12 is important for the differentiation of T_H1 cells with an important function in host defense against intracellular pathogens. In response to IL-4, naïve T cells differentiate into T_H2 cells, which play a crucial role in anti-parasite and humoral immunity. TGF-β together with IL-6 and IL-23 instruct naïve T cells to develop into T_H17 cells that mediate immunity against fungi and extracellular bacteria. In the absence of inflammatory cytokines, TGF-β promotes naïve T cells to differentiate into Foxp3-expressing iT_{reg} cells for the maintenance of immune tolerance.

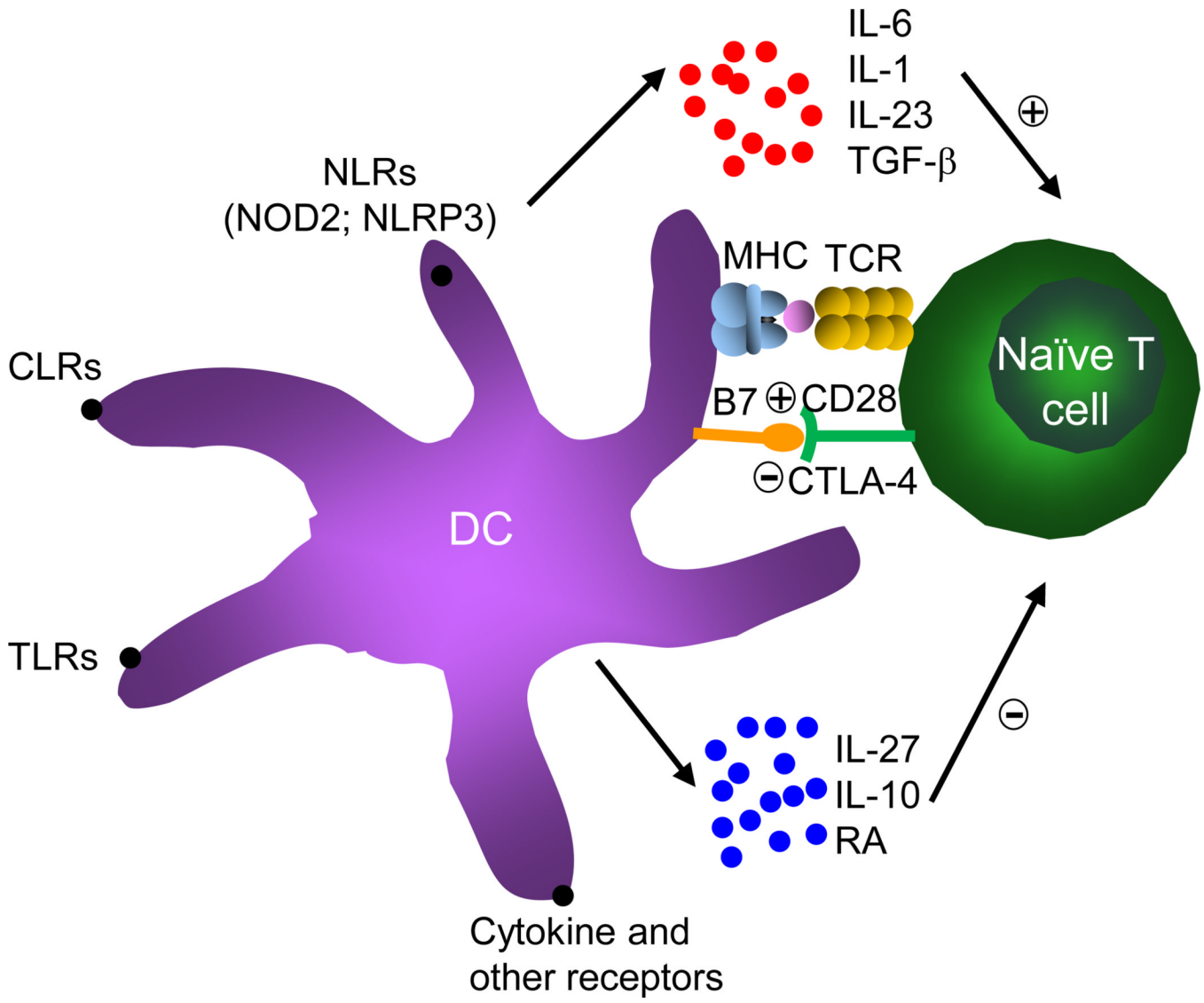

Figure 2. DC-derived innate signals instruct T_H17 cell differentiation

DCs sense pathogens or other stimuli *via* various cell surface receptors, including TLRs, CLRs, NLRs, cytokine receptors and other immunomodulatory receptors. DCs activated by these stimuli then present MHC bearing antigen-specific peptides to engage TCRs on naïve T cells. Upon stimulation, DCs also upregulate costimulatory molecules B7 to bind the corresponding receptors (CD28 or CTLA-4) expressed by T cells. Moreover, activated DCs produce positive (red color) or negative (blue color) T_H17-polarizing cytokines and non-cytokine mediators to regulate T_H17 cell differentiation.

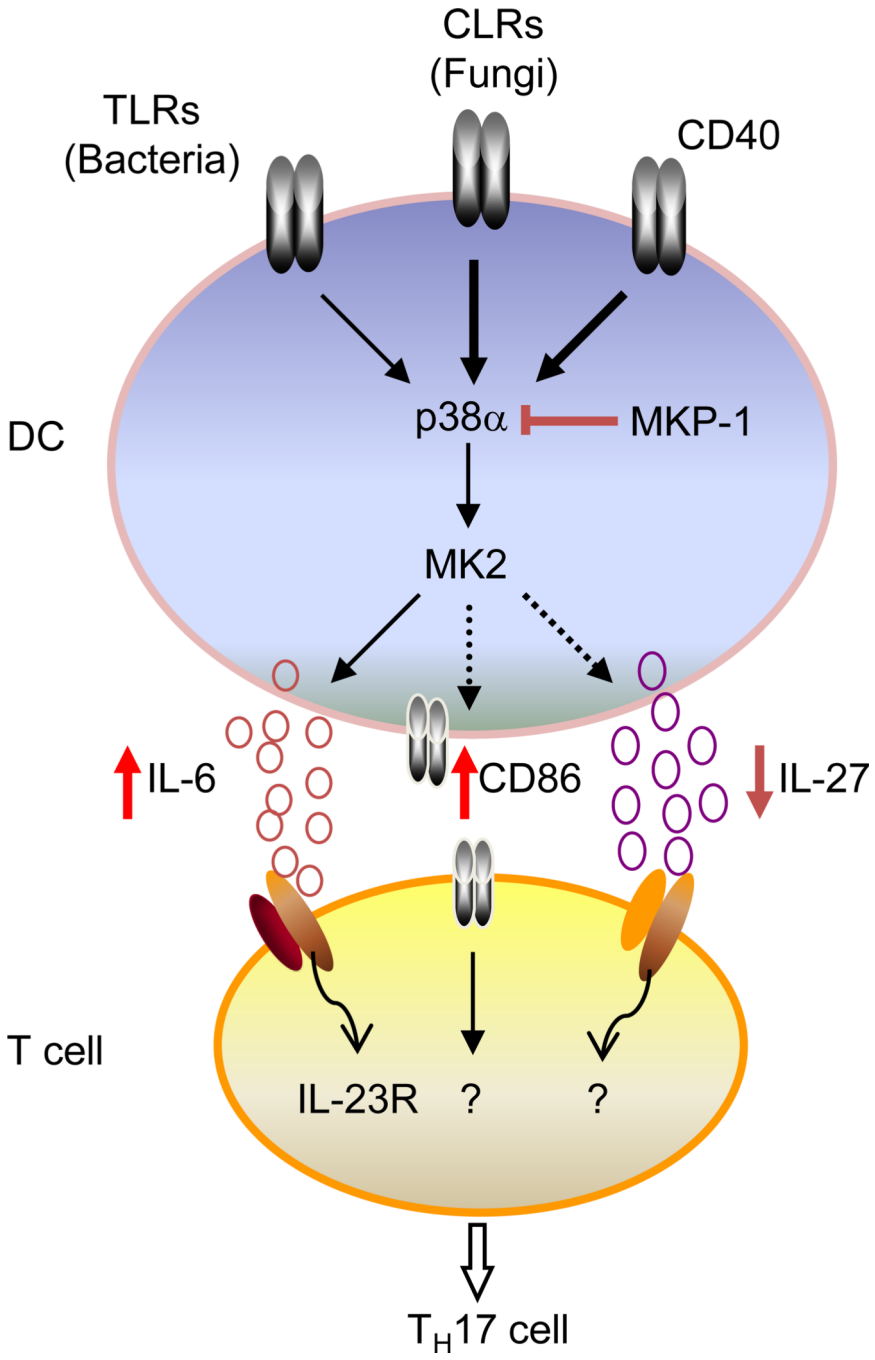

Figure 3. p38α MAPK/MKP-1 signaling axis programs DCs to regulate T_H17 cell differentiation

p38α in DCs integrates signals from TLRs (e.g., from bacteria), CLRs (e.g., from fungi) and CD40. Following stimulation, p38α activates its downstream targets including MK2 and other factors to regulate the expression of IL-6, IL-27 and CD86, which then deliver the signals to responding T cells for their differentiation into the T_H17 lineage. One important target for IL-6 in T cells is IL-23R whose induction further potentiates the T_H17 cell differentiation. Conversely, the phosphatase MKP-1 downregulates p38α activity in DCs, thereby suppressing T_H17 cell differentiation.